FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
212136US0PCT	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
09/926055	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/EP00/00745	31 January 2000
PRIORITY DATE CLAIMED	
25 February 1999	

TITLE OF INVENTION
ANTITUMOUR SYNERGISTIC COMPOSITION

APPLICANT(S) FOR DO/EO/US
GERONI Cristina et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice for Consideration of Documents Cited in International Search Report/Notice of Priority
PCT/IB/304
PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926055	PCT/EP00/00745	212136US0PCT

24. The following fees are submitted:.	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	10 - 20 =	0	x $18.00	$0.00
Independent claims	1 - 3 =	0	x $80.00	$0.00
Multiple Dependent Claims **(check if applicable).**			☐	$0.00

TOTAL OF ABOVE CALCULATIONS =	$860.00
Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00
SUBTOTAL =	$860.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00
TOTAL NATIONAL FEE =	$860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	$0.00
TOTAL FEES ENCLOSED =	$860.00
Amount to be: refunded	$
charged	$

a. ☒ A check in the amount of **$860.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Aug. 22 2001
DATE

212136US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

CRISTINA GERONI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLICATION:
(Based on PCT/EP00/00745)

FILED: HEREWITH :

FOR: ANTITUMOUR SYNERGISTIC :
COMPOSITION

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

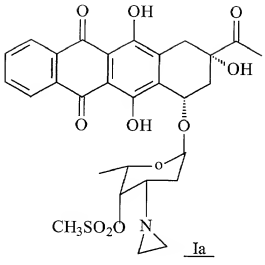
Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

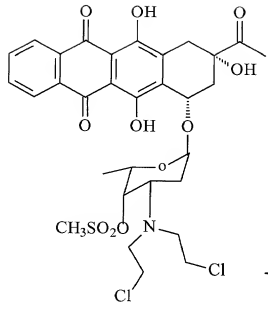
Please cancel Claims 7-9.

Please amend the claims as shown on the marked-up copy following this amendment to read as follows.

1. (Amended) A product comprising an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antineoplastic topoisomerase II inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. The product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

3. The product according to claim 1 wherein the topoisomerase II inhibitor is etoposide.

4. The product according to claim 1 wherein the topoisomerase II inhibitor is doxorubicin.

Please add the following new claims.

10. (New) A method of treating a mammal, including a human, for tumors comprising administering to said mammal an anthracycline of formula Ia or Ib as claimed in Claim 1, and an anti-neoplastic topoisomerase II inhibitor.

11. (New) The method as claimed in Claim 10 wherein the topoisomerase II inhibitor is etoposide or doxorubicin.

12. (New) A method of treating or preventing metastasis in a mammal, including a human, comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in Claim 1 and an antineoplastic topoisomerase II inhibitor.

13. (New) A method of treating a tumor in a mammal, including a human, by inhibiting angiogenesis comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in Claim 1 and an antineoplastic topoisomerase II inhibitor.

REMARKS

Claims 1-6 and 10-13 are active in the present application. Claims 1-4 have been amended to remove multiple dependencies and for clarity. Claims 10-13 are new claims. Support for new claims is found in the original claims and in the specification, for example on page 2, line 20-26 and page 4, lines 9-19. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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Marked-Up Copy
Serial No:

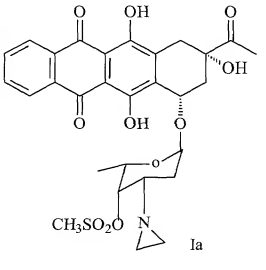
Amendment Filed on: 08/22/01

IN THE CLAIMS

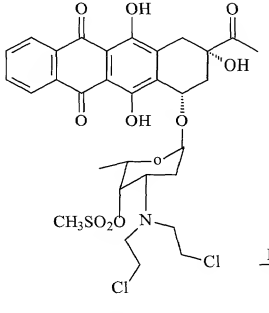
Claims 7-9 - (Cancelled).

Please amend the claims as follows.

--1. (Amended) [Products containing] A product comprising an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antineoplastic topoisomerase II inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. [Products] The product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

3. [Products] The product according to claim 1 [or 2] wherein the topoisomerase II inhibitor is etoposide.

4. [Products] The product according to claim 1 [or 2] wherein the topoisomerase II inhibitor is doxorubicin.--

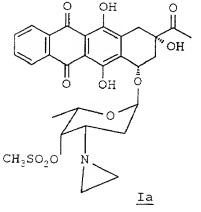
Claims 10-13 - (New).

Antitumour Synergistic Composition

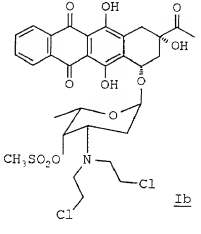
The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and a topoisomerase II inhibitor, having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib :



Ia



Ib

- an antineoplastic topoisomerase II inhibitor, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N^7 position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance

to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Topoisomerase II inhibitors are described in various scientific publications. The main representatives of this wide class of drugs are: the anthracycline derivatives such as doxorubicin, daunorubicin, epirubicin, nemorubicin and idarubicin; the podophyllotoxin compounds etoposide and teniposide; the anthraquinone derivative like mitoxantrone and amsacrine. See for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 452-467. Doxorubicin and etoposide are the preferred topoisomerase II inhibitors to be used in the present invention. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antineoplastic topoisomerase II inhibitor as defined above and an alkylating anthracycline of formula Ia or Ib, as defined

above, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a topoisomerase II inhibitor to mammals, including human.

By the term "administered " or "administering" as used herein is meant parenteral and /or oral administration. By "parenteral" is meant intravenous, subcutaneus and intramuscolar administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the compound with the topoisomerase II inhibitor activity, for example of the anthracycline or etoposide class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the alkylating anthracycline of formula Ia or Ib being utilized, the particular formulation of the topoisomerase II inhibitor, such as one of the anthracycline or etoposide class, being utilized, the particular tumor model being treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the topoisomerase II inhibitor the course

of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 10 to about 500 mg/m^2 of body surface area. The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor in the prevention or treatment of metastasis or for the treatment of tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis .

As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and a topoisomerase II inhibitor, such as an anthracycline or etoposide derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and of the topoisomerase II inhibitor and thus yields the most effective and least toxic treatment for tumors. The superadditive actions of the combination preparation of the present invention are shown for instance by the following *in vivo* tests, which are intended to illustrate but not to limit the present invention.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with etoposide.

At the dose of 30 mg/kg of etoposide alone (day +3) and at the dose of 1 mg/kg of Ia alone (days +1,2) were associated, without toxicity, with ILS% values of 100 and 67, respectively. Combining etoposide and Ia at the same doses with the same schedule an increase of activity with ILS% values of 450 was observed, indicating a synergistic effect.

Table 2 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with doxorubicin. At the dose of 13 mg/kg of doxorubicin alone (day +3) and at the dose of 1.5 mg/kg of Ia alone (days +1,2) were associated, without toxicity, with ILS% values of 50 and 67, respectively. Combining doxorubicin and Ia at the same doses with the same schedule an increase of activity with ILS% values of 150 was observed, indicating a synergistic effect.

For these experiments Ia was solubilized in [Cremophor® /EtOH= 6.5:3.5]/[normal saline]=20/80 v/v, while standard etoposide pharmaceutical preparation and doxorubicin solubilized in water were used.

Table 1: Antileukemic activity against disseminated L1210[1] murine leukemia of Ia in combination with Etoposide

Compound	Treatment schedule	Dose[2] (mg/kg/day)	ILS%[3]	Tox [4]	LTS[5]
Ia	iv +1,2	1	67	0/10	0/10
Etoposide	iv +3	30	100	0/10	0/10
Ia + Etoposide	iv +1,2 iv +3	1 + 30	450	0/10	4/10

Table 2: Antileukemic activity against disseminated L1210[1] murine leukemia of Ia in combination with Doxorubicin

Compound	Treatment schedule	Dose[2] (mg/kg/day)	ILS%[3]	Tox [4]	LTS[5]
Ia	iv +1,2	1.5	67	0/10	0/10

Doxorubicin	iv +3	13	50	0/10	0/10
Ia + Doxorubicin	iv +1,2 iv +3	1.5 + 13	150	0/10	3/10

1) L1210 leukemia cells (10^5/mouse) are injected iv on day 0.

2) Treatment is given starting on day 1 after tumor transplantation (day 0).

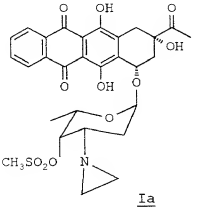
3) Increase in life span: [(median survival time of treated mice/median survival time of controls)x 100]-100

4) Number of toxic deaths/number of mice.

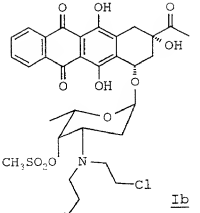
5) Long Term Survivors (>60 days) at the end the experiment.

Claims

1. Products containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antineoplastic topoisomerase II inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. Products according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

3. Products according to claim 1 or 2 wherein the topoisomerase II inhibitor is etoposide.

4. Products according to claim 1 or 2 wherein the topoisomerase II inhibitor is doxorubicin.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase II inhibitor.

6. A composition according to claim 5 wherein the topoisomerase II inhibitor is doxorubicin or etoposide.

7. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase

II inhibitor in the preparation of a medicament for use in the treatment of tumors.

8. Use according to claim 7 wherein the topoisomerase II inhibitor is etoposide or doxorubicin.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase II inhibitor in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ANTITUMOUR SYNERGISTIC COMPOSITION

the specification of which

- ☐ is attached hereto.
- ☐ was filed on _____ as
  Application Serial No. _____
  and amended on _____.
- ☐ was filed as PCT international application
  Number PCT/EP00/00745
  on 31 January 2000,
  and was amended under PCT Article 19
  on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
9904387.9	Great Britain	25 February 1999	☑ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Martin M. Zoltick, Reg. No. 35,745; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; and Paul E. Rauch, Reg. No. 38,591; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00 Cristina Geroni
NAME OF FIRST SOLE INVENTOR

Residence: Via Correggio, 48
20149 Milan (IT)

Signature of Inventor

Citizen of: Italy ITX

Post Office Address: the same as above

24 July 2001
Date

2-00 Marina Ripamonti
NAME OF SECOND JOINT INVENTOR

Residence: Viale Fulvio Testi, 91
20162 Milan (IT)

Signature of Inventor

Citizen of: Italy I.IX

Post Office Address: The same as above

24 July 2001
Date

3-00 Michele Caruso
NAME OF THIRD JOINT INVENTOR

Residence: Via Desiderio, 3
20131 Milan (IT)

Signature of Inventor

Citizen of: Italy I.IX

Post Office Address: The same as above

24 July 2001
Date

4-00 Antonino Suarato
NAME OF FOURTH JOINT INVENTOR

Residence: Via Degli Imbriani, 39
20158 Milan (IT)

Signature of Inventor

Citizen of: Italy I.IX

Post Office Address: The same as above

24 July 2001
Date

NAME OF FIFTH JOINT INVENTOR

Residence:

Signature of Inventor

Citizen of:

Post Office Address:

Date